

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21055

CHEMISTRY REVIEW(S)

DIVISION OF ONCOLOGY DRUG PRODUCTS
Original NDA Review of Chemistry, Manufacturing, and Controls

NDA #: 21-055 **CHEMISTRY REVIEW #:** 2 **REVIEW DATE:** December 23, 1999

SUBMISSION TYPE	DOC. DATE	CDER DATE	ASSIGNED DATE
Original	June 22, 1999	June 23, 1999	June 30, 1999
Amendment (BC)	December 8, 1999	December 9, 1999	December 14, 1999
Amendments (BC)	December 21, 1999	December 22, 1999	December 22, 1999

NAME & ADDRESS OF APPLICANT:

Ligand Pharmaceuticals Inc. -
 10275 Science Center Drive
 San Diego, CA 92121-1117

DRUG PRODUCT NAME:

Proprietary:
 Nonproprietary/USAN:

Targretin® Capsule
 Bexarotene (This name was adopted by the
 USAN Council, correspondence of 3/25/98)
 LGD1069, LG100069
 1P

Code Name/Number:
 Chem. Type/Ther. Class:

PHARMACOL. CATEGORY/INDICATION:

Activation of three retinoid X receptors (RXRα,
 β, γ) Cutaneous T-cell lymphoma (CTCL)
 Soft Gelatin Capsule
 75mg/capsule

DOSAGE FORM:

STRENGTHS:

ROUTE OF ADMINISTRATION:

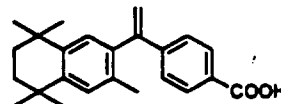
DISPENSED:

Oral

☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA (M.F.), MOLECULAR WEIGHT (M.W.):

CAS Name: 4-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl-2-naphthalenyl) ethenyl]
 benzoic acid (see attached USAN publication)
 Other Chemical Name: p-[1-(5,6,7,8-tetrahydro-3,5,5,8,8-pentamethyl 2-naphthyl)vinyl]-benzoic
 acid
 Common Name: Not available
 CAS Number: 153559-49-0
 Code Number: LGD1069, LG100069
 M.F.: C₂₄H₂₈O₂
 M.W.: 348.48



SUPPORTING DOCUMENTS:

INDs: IND []

DMFs:

DMF No.	Holder Name	LOA date	Subject	Status	Date Reviewed	Reference in this review
DMF		1/29/99 (page 202, v1.4)	Tamper-evident, foil innerseal M-1	Adequate	3/21/96	Reviewed by HFD-570
DMF		6/4/99 (page 201, v1.4)	Child-resistant cap	Adequate	4/27/99	Reviewed by HFD-510
DMF		1/15/98 (page 200, v1.4)	Round, 200cc, white HDPE bottle	Adequate*	6/12/92, 4/16/99, 5/4/99, 6/9/99, 8/11/99	Reviewed by HFD-120, HFD-510, HFD-570, HFD-633
DMF		2/23/99 (page 196, v1.4)	Opacode® blue edible ink S-1-10551 (page 4026 in DMF)	Adequate	12/23/99	Reviewed by HFD-150
DMF		5/13/99 (page 195, v1.4)	Preparation of gelatin mass used for the	Adequate	12/23/99	Reviewed by HFD-150

			manufacture of Targretin 75mg soft gelatin capsule			
DMF	LOA dated 12/11/98 (page 117, v1.3)					
DMF	(LOA dated 1/14/99 (page 203, v1.4)					
*Several chemistry reviews on different sizes and shapes of HDPE bottles for a solid oral dosage form have been noted and the reviews found acceptable.						

CONSULTS:

EER for

Trademark consultation was requested under IND [] on 1/16/97. Targretin® was found acceptable on 2/18/98.

Biopharm consultation was initiated on 10/1/99 concerning dissolution specifications and its method. Acceptable on 12/16/99 with change of the paddle speed from

Micro consultation, not applicable

Environmental assessment, Exemption is requested. Granted.

Stability data consultation, Not needed.

Method validation, Pending for initiation.

REMARKS/COMMENTS:CONCLUSIONS & RECOMMENDATIONS:

All CMC deficiencies were addressed satisfactorily in these amendments. Approval of this NDA is recommended from the standpoint of CMC. An expiration dating period of 12 months for the drug product manufactured from both sources [] is granted at this time.

The following CMC comments should be included in an action letter to be prepared:

- 1) An expiration dating period of 12 months for the drug product manufactured from both sources of the drug substance [] is granted at this time.
- 2) We remind your commitment to report a validation report concerning indene impurity within 6 months from the date of approval.
- 3) An approved paddle speed for the regulatory dissolution methods is 50rpm.
- 4) Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

cc:

Orig. NDA 21-055
HFD-150/Division File
HFD-150/ACHapman
HFD-150/SKim
HFD-150/RWood
HFD-810/HPatel
HFD-810/JSimmons
R/D Init. by: _____
filename: N21055.orl

/S/

Sung K. Kim, Ph.D.,
Review Chemist, HFD-150

/S/ 12-23-99

A. Chapman
NOV 29

DIVISION OF ONCOLOGY DRUG PRODUCTS
Original NDA Review of Chemistry, Manufacturing, and Controls

<u>NDA #:</u> 21-055	<u>CHEMISTRY REVIEW #:</u> 1	<u>REVIEW DATE:</u> November 26, 1999
<u>SUBMISSION TYPE</u>	<u>DOC. DATE</u>	<u>CDER DATE</u> <u>ASSIGNED DATE</u>
Original	June 22, 1999	June 23, 1999 June 30, 1999
Amendment (NC)	July 12, 1999	July 14, 1999 July 23, 1999
Amendment (NC)	September 16, 1999	September 17, 1999 September 21, 1999

NAME & ADDRESS OF APPLICANT:

Ligand Pharmaceuticals Inc.
10275 Science Center Drive
San Diego, CA 92121-1117

DRUG PRODUCT NAME:

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Nonproprietary/USAN:

Targretin® Capsule
Bexarotene (This name was adopted by the USAN Council, correspondence of 3/25/98)
LGD1069, LG100069
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Code Name/Number:
Chem. Type/Ther. Class:

PHARMACOL. CATEGORY/INDICATION:

Activation of three retinoid X receptors (RXR α , β , γ)
Cutaneous T-cell lymphoma (CTCL)

DOSAGE FORM:

Soft Gelatin Capsule

STRENGTHS:

75mg/capsule

ROUTE OF ADMINISTRATION:

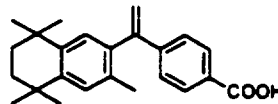
Oral

DISPENSED:

☒ Rx ☐ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA(M.F.), MOLECULAR WEIGHT(M.W.):

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Other Chemical Name: 4-[1-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)ethenyl]-benzoic acid
Common Name: Not available
CAS Number: 153559-49-0
Code Number: LGD1069, LG100069
M.F.: C₂₄H₂₈O₂
M.W.: 348.48



SUPPORTING DOCUMENTS:

INDs: IND []

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DMF		6/4/99 (page 201, v1.4)	Child-resistant cap	Pending for review		
DMF		1/15/98 (page 200, v1.4)	Round, 200cc, white HDPE bottle	Pending for review		
DMF		2/23/99 (page 196, v1.4)	Opacode® blue edible ink S-1-10551 (page 4026 in DMF)	Pending for review		

DMF		5/13/99 (page 195, v1.4)	Preparation of gelatin mass used for the manufacture of Targretin 75mg soft gelatin capsule	Adequate	11/10/99	Reviewed by HFD-150
DMF	LOA dated 12/11/98 (page 117, v1.3)					
DMF	LOA dated 1/14/99 (page 203, v1.4)					

RELATED DOCUMENTS (if applicable): N/A

CONSULTS:

EER for

Trademark consultation was requested under IND on 1/16/97. Targretin® was found acceptable on 2/18/98

Biopharm consultation was initiated on 10/1/99 concerning dissolution specifications and its method. Pending

Micro consultation, not applicable

Environmental assessment, Exemption is requested. Granted.

Stability data consultation, Pending for initiation

Method validation, Pending for initiation.

REMARKS/COMMENTS:

CONCLUSIONS & RECOMMENDATIONS:

CMC deficiencies were noted in this application. This NDA is approvable pending for satisfactory response to the deficiencies indicated in the draft letter.

ISR
Sung K. Kim, Ph.D.,
Review Chemist, HFD-150

cc:

Orig. NDA 21-055

HFD-150/Division File

HFD-150/ACHapman

HFD-150/SKim

HFD-150/RWood

HFD-810/HPatel

HFD-810/JSimmons

R/D Init. by: *IS/*

11-29-99

filename: N21055.org

(1st draft 11/12/99, revised 11/26/99)